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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,722	11/19/2001	Avi J. Ashkenazi	P2730P1C63	1427

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,722	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *119-138* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Preliminary Amendment, submitted 12 November 2001, and the Information Disclosure Statement, submitted 31 May 2002, have been entered. Claims 1-118 have been cancelled. Claims 119-138 have been entered.

Claims 119-138 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, in paragraph 2923. All URL's should be removed from the Specification. Applicant may refer to web sites by non-executable name only. See MPEP § 608.01 (p).

Appropriate correction is required.

Continuity

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: Most Provisional patent applications listed in the first paragraph of the instant specification do not list or refer to: SEQ ID NO: 351, SEQ ID NO: 350, PRO1153, or Figure 246. Therefore, for this Office Action, the filing date of 19 November 2001 is considered as the priority date.

Claim Rejections/Objections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

The following is a quotation of 35 U.S.C. 101:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 119-138 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to nucleotides which encode a polypeptide of 370 amino acids (see Figure 246, SEQ ID NO: 351 and 350). Further claim limitations are presented to isolated nucleic acids having at least 80% sequence identity to a nucleic acid encoding the polypeptide of SEQ ID NO: 350 or the polypeptide lacking its associated signal peptide. Claims are also presented encompassing vectors and cells comprising nucleic acids having at least 80% sequence identity to SEQ ID NO: 351. However, the specification does not disclose a function for the nucleotide of SEQ ID NO: 351, encoding the polypeptide of SEQ ID NO: 350, in the context of the cell or organism.

No well-established utility exists for newly isolated complex biological molecules. However, the specification asserts the following as credible, specific and substantial patentable

utilities for the claimed putative polynucleotide and polypeptide encoded by the claimed polynucleotide:

1) To make hybridization probes to detect the polynucleotide of SEQ ID NO: 351 (paragraph 352).

2) To produce the PRO1153 polypeptide and fragments.

3) For use in chromosome mapping (paragraph 3394).

4) For use in the construction of "knock-in" or "knock-out" organisms (paragraph 3408).

5) For making antisense oligonucleotides (paragraph 3409).

6) In assays to screen for compounds capable of modifying the interaction between receptor and ligand.

7) To make antibodies to the polypeptide encoded by the polynucleotide of SEQ ID NO: 350.

8) In tissue typing (paragraph 3413).

Each of these shall be addressed in turn:

1) To make hybridization probes to detect the polynucleotide of SEQ ID NO: 351.

This asserted utility is credible but not substantial or specific. Hybridization probes and primers can be designed from any polynucleotide sequence. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) To produce the PRO1153 polypeptide and fragment. This asserted utility is also credible and substantial, but not specific. Many nucleotide sequences can be used to make polypeptides. However, if the specification discloses nothing specific and substantial about the polynucleotides or polypeptides, both the polynucleotides and polypeptides produced have no patentable utility.

3) For use in chromosome mapping. This asserted utility is credible, but it is neither substantial nor specific. However, probes and primers can be designed from any polynucleotide sequence and used for chromosomal localization of the gene of interest, and thus the asserted utility is not specific. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) For use in the construction of "knock-in" or "knock-out" organisms. This asserted utility is credible but not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated PRO1153 gene. Significant further experimentation would be required of the skilled artisan to identify any such a disease. The specification discloses nothing about the phenotypic result when the PRO1153 gene is "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) For making antisense oligonucleotides. This asserted utility is credible but not specific or substantial. Such can be performed for any polynucleotide. Further, the specification does not disclose diseases or conditions associated with the PRO1153 gene. Significant further

experimentation would be required of the skilled artisan to identify individuals in need of antisense treatment to determine the route of administration of the antisense, as well as gene targets and quantity and duration of treatment. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) In assays to screen for compounds capable of modifying the interaction between receptor and ligand. This asserted utility is also credible and substantial but not specific. Such can be performed for any receptor-ligand pair. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method.

7) To make antibodies to the polypeptide encoded by the polynucleotide of SEQ ID NO: 351. This asserted utility is credible and substantial, but not specific. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, the polypeptide, the polynucleotide encoding the polypeptide and antibodies have no patentable utility.

8) *In tissue typing.* This asserted utility is credible but not substantial or specific. Such assays can be performed with any polypeptide encoded by a polynucleotide; thus, the asserted utility is not specific. Furthermore, the specification discloses a wide range of tissues that express the PRO1153 polypeptide. Applicant implies that this expression pattern supports a useful function of the polynucleotide encoding the PRO1153 polypeptide. However, patentable utility of tissue typing for the claimed polynucleotide encoding the PRO1153 polypeptide is not substantial, because one skilled in the art would not readily use the nucleotide sequences for tissue-typing in a real world sense as the protein is not specific to one tissue and is not associated

with any disease or disorder. This asserted utility is also not specific because numerous unrelated nucleotide sequences would also show a similar tissue typing pattern. In addition, evidence of mere expression in a tissue is not tantamount to a showing of a role for the polynucleotide of the present invention. It is not clear if expression of the polynucleotide of the present Invention is correlated with a specific change in physiology, for example, or with a disease state. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

9) To diagnose or treat cancer. Table 9B of the instant Specification sets forth the results of assays to determine the number of clone copies in a variety of tissues. A ΔCt of >1 was typically used as the threshold value for amplification scoring, as this represents a doubling of gene copy. The ΔCt values indicate that significant amplification of nucleic acid DNA59842-1502 encoding PRO1153 occurred in several epithelial tumors; The Specification implies that antagonists (e.g., antibodies) directed against the protein encoded by DNA59842-1502 (PRO1153) would be expected to have utility in cancer therapy.

However, a slight increase in clone copies in several tumor types is not indicative of a specific or substantial utility for PRO1153 for use as an agent to detect or treat cancer. A slight increase in clone numbers in a cancerous tissue is no doubt due to an increased number of chromosomes, a very common characteristic of cancerous and non-cancerous epithelial cells (see, for example: Hittelman, W., 2001, Ann. NY. Acad. Sci., 952: 1-12, especially pages 8 and 9, and; Crowell, et al, 1996, Cancer Epidemiol. 5: 631-637), not because PRO1153 plays a significant role in tumor formation or growth. The asserted utility is therefore not specific. Experiments confirming the specificity and substantial utility of PRO1153 in terms of mRNA

and protein expression were not performed. Antibodies against PRO1153 were not administered to animals to test their anti-cancer effects. Significant further experimentation would be required of the skilled artisan to determine whether PRO1153 is expressed in certain cancers to the extent that antagonists (e.g., antibodies) directed against the protein encoded by DNA59842-1502 (PRO1153) would be expected to have utility in cancer therapy. Thus, the asserted utility is not substantial. In addition, the Specification shows that gene copy number is increased in certain tumor tissue samples. However, it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the antibodies would be useful diagnostically or as a target for cancer drug development. For Example, Pennica et al (1998, PNAS 95: 14717-14722) disclose that:

"An analysis of WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient," (page 14722, second paragraph).

Furthermore, although the specification teaches that PRO1153 is expressed in several epithelial cancers (Table 9B), the state of the art is such that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript, and therefore cannot be correlated to antibody binding. Haynes et al, for example, studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels (Haynes et al., 1998, Electrophoresis 19:1862-1872). That research group found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold (pg 1863, paragraph 2, Figure 1). Therefore, one skilled in the art

cannot predict that the PRO1153 mRNA transcript levels determined in various cancerous tissues are indicative of PRO1153 polypeptide expression in cancerous cells. Undue experimentation is required by the skilled artisan to detect and quantify PRO1153 polypeptide expression in all possible tumor tissues/cells, other than lung or epithelial cancer.

Claims 119-138 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed polynucleotides encoding SEQ ID NO: 351 and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description.

Claims 119-138 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are directed to nucleotide(s) which encode a polypeptide of 370 amino acids (see Figure 246). Further claim limitations are presented to isolated nucleic acids having at least 80% sequence identity to a nucleic acid encoding the polypeptide of SEQ ID NO: 350, or the polypeptide of SEQ ID NO: 350 lacking its associated signal peptide. Claims are also presented encompassing vectors and cells comprising nucleic acids having at least 80%, at least 90% and at least 95% sequence identity to SEQ ID NO: 351.

The specification teaches a polynucleotide (SEQ ID NO: 350) and a polypeptide (SEQ ID NO: 351). However, the specification does not teach functional or structural characteristics of all claimed polynucleotides. The description of one polynucleotide encoding a PRO polypeptide (SEQ ID NO: 351) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides.

To provide evidence of enablement of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure

in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of all claimed polynucleotides and all encompassed PRO polypeptides, and therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of use. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The nucleotide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 350 and a polypeptide comprising the amino acid sequence of SEQ ID NO: 351, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, first paragraph – Deposit Rules

Claims 119-138 are also rejected under 35 U.S.C. § 112, first paragraph, as not complying with the enablement requirement. The invention appears to employ novel nucleic acid molecules (i.e., clone: DNA59842-1502). Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The Specification at paragraph 4840 indicates that the deposit was made under the Budapest treaty. However, Applicants have failed to provide a copy of the deposit receipt. If a deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit is <u>not</u> made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may

provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable. Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination. Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification.

The new address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 119-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 119-138 are rendered indefinite because of the phrase "extracellular domain." The metes and bounds of Claims 119-138 are indefinite in view of the instant Specification which implies and states that the polypeptide encoded by the claimed polynucleotide(s) is a secreted protein. Such an "extracellular domain" would be found in a cleaved transmembrane protein, for example, along with an intracellular domain, but is not recognized in secreted proteins since they are entirely "extracellular."

Claims 132 and 133 are rendered indefinite because of the phrase "stringent conditions," which is a conditional term. In other words, for example, some nucleic acids which are able to hybridize under stringent conditions would be unable to hybridize under non-stringent conditions. The metes and bounds of the claim, therefore, cannot be ascertained. This rejection can be overcome by supplying specific conditions, supported by the specification, which the Applicants consider "stringent," or by removing the indefinite phrase.

Claim Rejections- 35 USC § 102

The following are quotations of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 134 is rejected under 35 U.S.C. 102(b) as being unpatentable over Davies, et al, (1996, Accession No. HSU51280). Davies, et al, disclose a polynucleotide sequence which contains several lengths of nucleotides 10 or more bases long which are identical to 10-base segments of the PRO1153 polynucleotide in the instant application. This reference meets the limitations of Claim 43 of polynucleotides "at least 10 nucleotides in length."

Conclusion: Claims 119-138 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9246 (toll-free).

Elizabeth C. Kemmerer

SLW

3/16/04

ELIZABETH KEMMERER
PRIMARY EXAMINER